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TITLE: Development of Dietary Polyphenol Preparations for Treating Veterans with Gulf War Illness

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14. ABSTRACT

There are no treatments for Gulf War Illness (GWI) and there is an urgent need to develop novel interventions either to resolve underlying GWI mechanisms, or to alleviate major GWI clinical complications, particularly chronic fatigue, cognitive difficulties, muscle pain, as well as mood disturbances and sleep problems. Recent evidence from our group and from others revealed that certain dietary flavonoids may promote cognitive function and/or alleviate chronic fatigue. We hypothesized that dietary supplementation with a Flavonoid Rich Preparation (FRP), a combination of Concord Grape Juice (CGJ) and Grape Seed Polyphenolic Extract (GSPE) may help alleviate clinical complications of GWI, particularly chronic fatigue and/or cognitive dysfunction. We propose to test the feasibility of dietary supplementation with FRP in Veterans with GWI, and to gather evidence supporting the efficacy of FRP in alleviating GWI-associated cognitive deficits and chronic fatigue. **Purpose:** To conduct a randomized, double-blind Phase I/IIA study to explore long-term dose compliance, safety, tolerability of FRP and to assess the efficacy of FRP in improving cognition function and alleviating chronic fatigue in Veterans with GWI. **Scope:** Evidence gathered by our proposed studies will provide the necessary proof of principle data and support future development of broader efficacy studies of a specific, readily available nutritional supplementation regimen, FRP, for treating Veterans with GWI. **Progress:** In fiscal year 3, we continued recruitment through the DMDC-generated database by sending introductory letters accompanied by follow-up calls two weeks later. Due to financial constraints, we closed the protocol to new enrollment on July 19th, 2018 (the date of VANJHCS Continuing Review). At the time of study closure, we had sent letters to 777 potential participants. Of those 777, we screened 72 potential participants with 46 of them screening eligible. Of the 46 who were eligible to continue, 36 came to the VANJHCS to be consented and enrolled in the study with 24 of them already completing the 24-week protocol. We will allow those enrolled prior to the enrollment closure date to finish the protocol before beginning our data analysis; estimated date of final endpoint is January 3rd, 2019.

15. SUBJECT TERMS NONE LISTED

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1. INTRODUCTION

An estimated 174,300 to 230,000 US military service members deployed to Iraq and Afghanistan are affected by Gulf War Illness (GWI). GWI is characterized by the persistent presentation of multiple functional symptoms involving a combination of diverse complaints centering on chronic fatigue, cognitive difficulties, muscle pain, as well as mood disturbances and sleep problems that are not explained by established medical diagnoses. While the etiology of the GWI symptom complex is not known, GWI clinical complications typically persist over long-terms, cause significant pain and suffering, and interfere with the ability of affected Veterans to successfully integrate back into the civilian society. There are no treatments for GWI and there is an urgent need to develop novel interventions either to resolve underlying GWI mechanisms, or to alleviate major GWI clinical complications. Recent evidence from our group and from others revealed/highlighted the potential value of flavonoids, a subclass of organic chemical called polyphenols that are abundantly found in some plants and common dietary preparations, may help alleviate chronic fatigue and preserve against cognitive functions. Based on this, our overall goal is to test the potential efficacy of dietary supplementation with a Flavonoid-Rich Preparation (FRP) to alleviate clinical complications in Veterans with GWI. In particular, we proposed to conduct a randomized, double-blind Phase I/IIA study to explore long-term dose compliance, safety, tolerability of FRP and to assess the efficacy of FRP (Concord grape juice) in improving cognition function and alleviating chronic fatigue in Veterans with GWI. Evidence gathered by our proposed studies will provide the necessary proof of principle data and support future development of broader efficacy studies of a specific, readily available nutritional supplementation regimen, FRP, for treating Veterans with GWI.

2. KEYWORDS

Gulf War Illness
Polyphenol
Flavonoids
Flavonoid-Rich Preparation
Chronic fatigue
Cognitive difficulties
Muscle pain
Mood disturbances
Sleep problems

3. ACCOMPLISHMENTS

- ***Major goals of the project***

Obtain IND/IRB approval (Year 0 to 0.5)

- obtain FDA IND approval
- Obtain local institutional IRB approval (from the Icahn School of Medicine at Mount Sinai and from the Department of Veterans Affairs, New Jersey Health Care System (DVANJHCS)
- Obtain approval from the U.S. Army Human Research Protection Office (HRPO)

Recruit 60 volunteers (Year 0.5 to 1.17)

- randomized volunteers into a treatment and a placebo arm, n=30 per arm
- complete baseline clinical assessments
- collect and bank baseline blood specimen

FRP treatment (Year 0.7 to 1.5)

- initial dose-escalation finding phase (6 weeks) followed by a stable treatment dose (18 weeks)
- complete clinical assessments during and post treatment
- collect and bank blood post treatment

Complete analysis of blood polyphenol contents (Year 0.5 to 1.7)

Complete data analysis and manuscript preparation (Year 1.8 to 5)

- ***Accomplishments under these goals***

We originally proposed to treat GWI subjects using a FRP comprised of combined Concord grape juice and a grape seed polyphenol extract. We obtained IND approval from the FDA (IND 123889) to conduct this trial using the FRP in veterans with GWI. Moreover, we submitted an IRB application to the Department of Veterans Affairs, New Jersey Health Care System (DVANJHCS) at East Orange, New Jersey for recruiting GWI cases for the study, treating and monitoring participant subjects, and collecting and banking de-identified plasma specimens from these subjects for subsequent biochemical analysis by investigators at the Icahn School of Medicine (ISMMS). We also submitted an IRB application to ISMMS for conducting biochemical analysis of banked de-identified blood specimen that will be provided by DVANJHCS.

Since submission of our initial IND and IRB documents, our research team decided that, to promote better compliance over the long term, we should amend our protocol by removing grape seed polyphenol extract from the protocol and treat GWI cases with a FRP comprised of only Concord grape juice. The range of Concord grape juice doses proposed is within the range of efficacy for improving cognitive function in the elderly, as was discussed in the application. This amendment does not change the goals and timelines in the SOW. But since we have removed grape seed polyphenol extract from the study, we have amended the SOW to reflect this modification. We have discussed this with our program officer, Mr. Brett Chaney, and he approved our proposed amendment. We submitted to FDA an amendment for using only Concord grape for our proposed studies in veterans with GWI and the amended protocol received FDA approval (IND 123889). We also submitted our amended protocol, using only Concord grape juice to the ISMMS IRB and the DVANJHCS IRB. The proposed amended protocol received ISMMS and DVANJHCS IRB approval. In our 1st DoD Annual Report, we have submitted our amended SOW, as well as documents from the FDA and from ISMMS and DVANJHCS IRBs confirming approval of our amended protocol.

As stipulated by both local institutional IRBs, we have since applied for and received annual re-approval of our protocol.

We have since obtained USAMRMC HRPO approval to procure investigatory reagents and begin the initial subject recruitment.

All study logs, policies, procedures, and data collection tools are now in place. Neuropsychological assessment instruments have been delivered as well as all other necessary study items. Research personnel have been appropriately trained to conduct research activities (screening, consenting, survey administration, neuropsychological testing, data entry, blood specimen processing).

All study team personnel at the clinical site (VANJHCS) are also in place:
Principal Investigator: Drew Helmer, MD, MS
Study staff: David Litke PhD (Psychologist)
Jan Einhorn, RN (Study Nurse)
Lydia Patrick-DeLuca, RN (Study Nurse – Back Up)
Nancy Eager (Phlebotomist – Back Up)
William Van Doren (Research Assistant)
Michelle Deluca (Research Assistant - Back Up)

By the end of fiscal year 2, we identified 400 potentially eligible Gulf War Veterans for recruitment and sent out 137 recruitment letters to those that lived within a 100-mile radius of the clinical site (VANJHCS). We screened 10 Veterans, with 7 being eligible for participation. Of these, 5 were enrolled while the remaining 2 were lost to follow-up/no longer interested.

During fiscal year 3, we sent out an additional 250 recruitment letters. We screened 33 Veterans, with 20 being eligible for participation. Of these, 15 were enrolled while the remaining 5 were lost to follow-up/no longer interested.

During the past year (fiscal year 4), we sent out a final 127 recruitment letters. We screened 29 Veterans, with 19 being eligible for participation. Of these, 16 were enrolled while the remaining 3 were lost to follow-up/no longer interested. Due to financial constraints, we closed the study to new enrollees on July 19th, 2018 (date of VANJHCS Continuing Review). All subjects enrolled will be allowed to complete the full 24-week protocol; our estimated date for the final study endpoint visit is January 3rd, 2019.

At time of enrollment closure, we had screened 72 Veterans total, with 46 of them being eligible for participation. Of these 46, 36 were consented / enrolled while the other 10 were lost to follow-up / no longer interested. Among the 36 who enrolled, 24 already completed the 24-week protocol.

Processed blood samples for the consented / enrolled participants are being stored securely within an ultra-low temperature freezer at the clinical site (VANJHCS). They will be shipped to Mt. Sinai for analysis upon completion of the final study endpoint.

- ***Opportunities for training and professional development the project provided***
  Nothing to Report

- ***How were the results disseminated to communities of interest?***
  Nothing to Report

- ***What do you plan to do during the next reporting period to accomplish the goals?***

We will complete the 24-week protocol with the remaining enrollees. After completion of final endpoint visit, processed blood samples will be shipped to Mt. Sinai for analysis. Data analysis and manuscript preparation will begin soon afterward.

4. IMPACT

- **What was the impact on the development of the principal discipline(s) of the project?**
  Nothing to Report

- **What was the impact on other disciplines?**
  Nothing to Report

- **What was the impact on technology transfer?**
  Nothing to Report

- **What was the impact on society beyond science and technology?**
  Nothing to Report

5. CHANGES/PROBLEMS

- **Changes in approach and reasons for change**
  Due to financial constraints, we closed recruitment with a final n=36 rather than the originally approved n=60.

- **Actual or anticipated problems or delays and actions or plans to resolve them**
  Nothing to Report

- **Changes that had a significant impact on expenditures**
  Nothing to Report

- **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
  Nothing to Report

- **Significant changes in use or care of human subjects**
  Nothing to Report

- **Significant changes in use or care of vertebrate animals.**
  Not applicable

- **Significant changes in use of biohazards and/or select agents**
  Nothing to Report

6. PRODUCTS

- **Publications, conference papers, and presentations**
  Nothing to Report

- **Journal publications.**
  Nothing to Report

- **Books or other non-periodical, one-time publications.**
  Nothing to Report

- **Other publications, conference papers, and presentations.**
  Presentation to the Gulf War Research Advisory Committee
  Presenter: Dr. Drew A. Helmer
  Date: September 29, 2015
  Presentation Title: Development of Dietary Polyphenol Preparations for Treating Veterans with Gulf War Illness

- **Website(s) or other Internet site(s)**
  ClinicalTrials.gov Identifier: NCT02915237
  Warrelatedillness.va.gov

- **Technologies or techniques**
  Nothing to Report

- **Inventions, patent applications, and/or licenses**
  Nothing to Report

- **Other Products**
  Using lessons learned from this current study, the Investigators submitted a grant proposal to the VA Clinical Science Research and Development (CSR&D) Gulf War Project aimed at investigating the feasibility and potential efficacy of dietary supplementation with a select Bioactive Dietary Polyphenol Preparation (BDPP) to alleviate cognitive dysfunction in Veterans with GWI.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

- **What individuals have worked on the project?**
  Dr. Giulio Pasinetti (PI, ISMMS): no change
  Dr. Drew Helmer (clinical PI, VA NJHCS): no change
  Dr. Lap Ho (co-investigator, ISMMS): no change
  Dr. David Litke (Neuropsychologist): no change
  Will Van Doren (Research Assistant): no change
  Jan Einhorn (Study Nurse): no change
  Nancy Eager (Phlebotomist): no change
  Yvette Blackbourne (Data Analyst): Left VANJHCS; removed from study personnel log.
  Michelle Deluca (Research Assistant Back-Up): no change

- **Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
  Nothing to Report

- **What other organizations were involved as partners?**
  Nothing to Report

8. SPECIAL REPORTING REQUIREMENTS

- **COLLABORATIVE AWARDS:** N/A
- **QUAD CHARTS:** N/A

9. APPENDICES: None